

We claim:

1. A method of sequence specific recombination of DNA in a eukaryotic cell, comprising
 - 5 a) introducing a first DNA sequence into a cell,
 - b) introducing a second DNA sequence into a cell, and
 - c) performing the sequence specific recombination by a bacteriophage lambda integrase Int.
- 10 2. Method of sequence specific recombination of DNA in a eukaryotic cell having a first DNA sequence in its genome, either naturally occurring or being introduced previously by DNA recombination, comprising the steps b) and c) defined in claim 1.
- 15 3. Method according to claim 1 or 2, wherein said first DNA sequence comprises an *attB* sequence according to SEQ ID NO:1 or a derivative thereof and said second DNA sequence comprises an *attP* sequence according to SEQ ID NO:2 or a derivative thereof.
- 20 4. Method according to claim 1 or 2, wherein said first DNA sequence comprises an *attL* sequence according to SEQ ID NO:3 or a derivative thereof and said second DNA sequence comprises an *attR* sequence according to SEQ ID NO:4 or a derivative thereof, wherein in step c) additionally a *Xis* factor is present.
- 25 5. Method according to anyone of claims 1 to 4, wherein additionally a third or a third and fourth DNA sequence comprising an *Int* gene or an *Int* gene and a *Xis* factor gene, respectively, is introduced into the cell.
- 30 6. Method according to claim 5, said third or said third and/or fourth DNA sequence further comprising a regulatory DNA sequence effecting a spatial and/or temporal expression of the *Int* gene and/or the *Xis* factor gene.
7. Method according to anyone of claims 1 to 6, wherein said *Int* is a modified integrase.

8. Method according to claim 7, wherein said modified Int is Int-h or Int-h/218.

9. Method according to anyone of claims 1 to 8, wherein in step c) additionally an "integration host factor" (IHF) is involved.

5 10. Method according to anyone of claims 1 to 9, said first and/or second DNA sequence further comprising DNA sequences effecting an integration of said first and/or second DNA sequence into the genome of the eukaryotic cells by homologous recombination.

10 11. Method according to anyone of claims 1 to 10, said first and/or second DNA sequence further comprising a nucleic acid sequence coding for a polypeptide of interest.

15 12. Method according to claim 11, wherein said polypeptide of interest is a structural protein, an endogenous or exogenous enzyme, a regulatory protein or a marker protein.

13. Method according to anyone of claims 1 and 3 to 12, wherein said first and second DNA sequence are introduced into the eukaryotic cell on the same DNA molecule.

20 14. Method according to anyone of claims 1 to 13, wherein said eukaryotic cell is a mammalian cell.

15. Method according to claim 14, wherein said mammalian cell is a human, simian, mouse, rat, rabbit, hamster, goat, bovine, sheep or pig cell.

25 16. Method according to anyone of claims 1 to 3 and 5 to 15, further comprising d) performing after a first sequence specific recombination of DNA according to the steps a) to c) or a) and b) without a Xis factor a second sequence specific recombination of DNA by an Int and a Xis factor.

30 17. Method according to claim 16, further introducing a further DNA sequence into said cells, the further DNA sequence comprising a Xis factor gene.

18. Method according to claim 17, wherein said further DNA sequence comprises further a regulatory DNA sequence effecting a spatial and/or temporal expression of said Xis factor gene.

5 19. The use of an *attB* sequence according to SEQ ID NO:1 or a derivative thereof and an *attP* sequence according to SEQ ID NO:2 or a derivative thereof, or an *attL* sequence according to SEQ ID NO:3 or a derivative thereof and an *attR* sequence according to SEQ ID NO:4 or a derivative thereof in a sequence specific recombination of DNA in eukaryotic cells.

10 20. Nucleic acid sequence according to SEQ ID NO:5 or a derivative thereof.

21. Vector, comprising a nucleic acid sequence according to SEQ ID NO:5 or a derivative thereof and a further nucleic acid sequence coding for a therapeutic gene or a

15 DNA fragment thereof.

22. Vector according to claim 21, wherein said therapeutic gene is the CFTR gene, ADA gene, LDL receptor gene, β globin gene, Factor VIII gene or Factor IX gene, alpha-1-antitrypsin gene or the dystropin gene or a gene fragment of one of said genes.

20 23. Vector according to claim 21 or 22, wherein said further nucleic acid sequence comprises further expression and/or transcription elements.

24. Vector according to anyone of claims 21 to 23 for the use as a medicament in the

25 human or veterinary medicine.

25. Use of a vector according to anyone of claims 21 to 23 for the manufacture of a medicament for the somatic gene therapy.

30 26. Eukaryotic cell, obtainable by subjecting said eukaryotic cell of claim 1 or 2 to the method according to anyone of claims 1 to 18.

27. Transgenic organism comprising at least one cell according to claim 26.

28. The organism according to claim 27, wherein said organism is a mouse, rat rabbit or hamster.

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